EVALUATION OF CLINICAL SEVERITY IN SICKLE CELL DISEASE

Bruce F. Cameron, MD, PhD, E. Christian, RN, PNA, Jeffrey S. Lobel, MD, and Marilyn H. Gaston, MD
Cincinnati, Ohio

For a severity classification of sickle cell disease to be accepted, it is necessary that clinicians agree upon relative disease severity between patients. This condition was shown to be satisfied for a randomly selected group of patients evaluated by four persons. All rank correlation coefficients between observer pairs were highly significant. Representative severity indices based on history and recent hospital events also correlated significantly with evaluator ranking. The results show that, in principle, a classification of sickle cell disease patients by severity is possible. Such a classification would be most useful to evaluate the prognostic significance of particular signs or symptoms, or the success of various treatments in affecting severity of disease.

Sickle cell disease is an inherited hemolytic anemia with a highly variable course and severity. In the evaluation of clinical status or prognosis for disease progression, and especially in the evaluation of therapeutic intervention, a precise assessment of the severity of the disease would be useful. There have been several suggestions for objective criteria to establish a general severity classification. If persons providing clinical care to such patients perceive relative disease severity in their patients in a concordant fashion, then in principle an objective severity index could be developed. If they do not, then agreement on such an index would be difficult.

Investigators have attempted to correlate several specific laboratory findings with the course of the disease. These include the level of fetal hemoglobin,[1] the proportion of irreversibly sickled cells,[2] associated glucose-6-phosphate dehydrogenase deficiency,[3] or platelet function[4] among others. There have also been proposals for a standard severity classification,[5,6] but these have not been widely accepted. The absence of a recognized method for defining severity hampers comparability of such studies.

In a setting in which a number of sickle-cell anemia patients are regularly seen, those responsible for their clinical treatment do recognize variations in severity. They can rank the patients according to their subjective perception of disease severity. This study is designed to examine this qualitative perception of severity in sickle cell disease for the full spectrum of clinical presentation, and to compare this ranking with representative quantitative indices determined by objective criteria.

The operating hypothesis may be stated as follows: If one wishes to objectively grade sickle cell disease severity, a prerequisite of such grading is that persons well acquainted with the patients being evaluated should agree upon the extent of

From the Cincinnati Comprehensive Sickle Cell Center, Children's Hospital Research Foundation, Cincinnati. Requests for reprints should be addressed to Dr. Bruce Cameron, Cincinnati Comprehensive Sickle Cell Center, Children's Hospital Research Foundation, Elland & Bethesda Avenues, Cincinnati, OH 45229.

their illness. If several such observers perceive the severity of illness in a group of patients in a differing order, then it will be difficult to devise a mutually acceptable objective index.

METHODS

Subjects

A total of 24 subjects were randomly selected, from a population of 133 patients receiving care at our institution, using patient chart numbers and a random number table.[7] This number of subjects was sufficient to include a broad range of clinical symptomatology and yet small enough for the evaluators to rank by severity. The study group ranged in age from 14 months to 21 years, with 12 males and 12 females. All were black Americans with diagnosis confirmed by hemoglobin electrophoresis on both cellulose acetate and citrate agar, and quantitation of fetal hemoglobin and hemoglobin A_2. Distribution by disease entity was 18 with homozygous sickle cell anemia, four with hemoglobin SC disease, and two with sickle-β+ thalassemia. This ratio (18:4:2) is not significantly different from that in our total patient population when tested by the chi-square statistic.

Subjective Ranking

Subjective ranking of the patients for relative severity of disease was done by four persons who have had a total of 18 patient contact years in the Comprehensive Sickle Cell Center, Cincinnati, Ohio. Evaluators were selected based upon their long-term clinical contact with the patients and their families. One was a pediatric hematologist, two were social workers, and one was a nurse practitioner. Social service was included because, in our setting, the social workers see the patients both at clinic visits and as inpatients, and are a working part of the clinical-care team. Each evaluator independently ranked the patients according to their perception of the severity of the disease, with the number "1" being most severe (ties were allowed). No time limit was set for the task, and there was an option of ranking extemporaneously or referring to the patient history. Evaluators were given no instructions or criteria for ranking, since the purpose of the study was to examine concordance of individual subjective impression of disease severity. One might expect them to use different criteria, but the test was designed to determine whether each evaluator sees a given patient as more or less severely affected than another. Patient ranks were rescored to account for ties, such that the range was 1 to 24 and the mean rank was 12.5. In addition, the ranking of each patient for all four evaluators was averaged. This average rank for each patient was adjusted to a 1 to 24 scale, rescored for ties.

Quantitative Indices

Representative quantitative indices for severity of sickle cell disease were determined by two methods which are used in this Center. The first index was based on a numerical score from the clinical history, using six major criteria selected as being reasonably inclusive of clinical manifestations: age at diagnosis, number of hospitalizations, number and types of crises, presence or absence of pneumococcal infection, major organ involvement, and failure to thrive.[8] Points were assigned to each category in rough proportion to the potential for patient mortality or morbidity. Point scores for each category and subdivisions are presented in Table 1.

The second index was simply a sum over the past year of days of hospitalization, number of emergency room visits, and number of units of transfused blood. This information could be obtained from summary records and did not require detailed chart review.

These quantitative indices for the patients were transformed to rank order. This ranking allowed a comparison of subjective severity and quantitative scoring by standard statistical methods.

RESULTS

Rankings were compared with each other, with the average rank, and with the quantitative severity index ranks by the Spearman rank correlation statistic.[9] Relative patient ranking by the four evaluators was generally concordant. Rank correlation between evaluator pairs was significant for all comparisons (Table 2). The correlation of individual evaluator ranks with the average rank is shown in Figure 1. All correlation coefficients are significant at least at the 0.1 percent level.

The correlations of the quantitative indices with each other and with the mean subjective ranking

TABLE 1. CLINICAL CLASSIFICATION CRITERIA

		Points
I.	Age at diagnosis	
	Less than 12 mo	3
	12-24 mo	2
	25 mo-5 yr	1
	More than 5 years	0
II.	Number of hospitalizations	
	5 or more	3
	2-4	2
	1	1
III.	Crisis	
	Sequestration	3
	Aplastic	2
	Thrombotic (requiring hospitalization)	1
IV.	Pneumococcal sepsis	3
V.	Major organ involvement	
	Cerebrovascular accident, pulmonary infarct, or retinopathy	3
	Pneumonia, renal or bone involvement, priapism, leg ulcer, or congestive heart failure	2
VI.	Failure to thrive	
	< 3 percentile, height and weight	3
	< 10 percentile	2
	< 25 percentile	1

are presented in Figure 2. These correlations are not as high as those of individual evaluators with the mean ranking, but are still significant at the 0.5 percent level.

DISCUSSION

It is clear from the data and correlations presented that our initial hypothesis is accepted. There is an essentially concordant subjective perception of severity of disease by individuals knowledgeable about the affected patients. There is a variable ranking of individual patients, as can be seen in Figure 1, but all rank correlations are significant. An average of rankings is probably a better estimation of patient severity, with highly significant correlations for each evaluator with the average rank.

Either of the quantitative indices used in this study also correlated with the average subjective ranking at least at the 0.5 percent level, although the correlation coefficient for Index I (clinical classification, Table 1) with the subjective grading is greater than that for Index II (hospitalization-transfusion count). Index II, based only on the most recent clinical events, might be expected not to be as good a quantitation of disease severity as Index I. The correlations of these indices with the subjective ranking do not differ sufficiently to choose one index over the other, although the better correlation with Index I suggests that the evaluators do integrate the entire course of the disease process into their evaluation of severity.

TABLE 2. RANK CORRELATION COEFFICIENTS (r_s—SPEARMAN) AND SIGNIFICANCE (P) LEVELS FOR SUBJECTIVE SEVERITY RANKING OF SICKLE CELL DISEASE PATIENTS

	JL	EC	AH	BM
JL	1.00			
EC	.50*	1.00		
AH	.54**	.58†	1.00	
BM	.62†	.48*	.79‡	1.00

*.02 < P < .01
**P < .01
†P < .005
‡P < .001

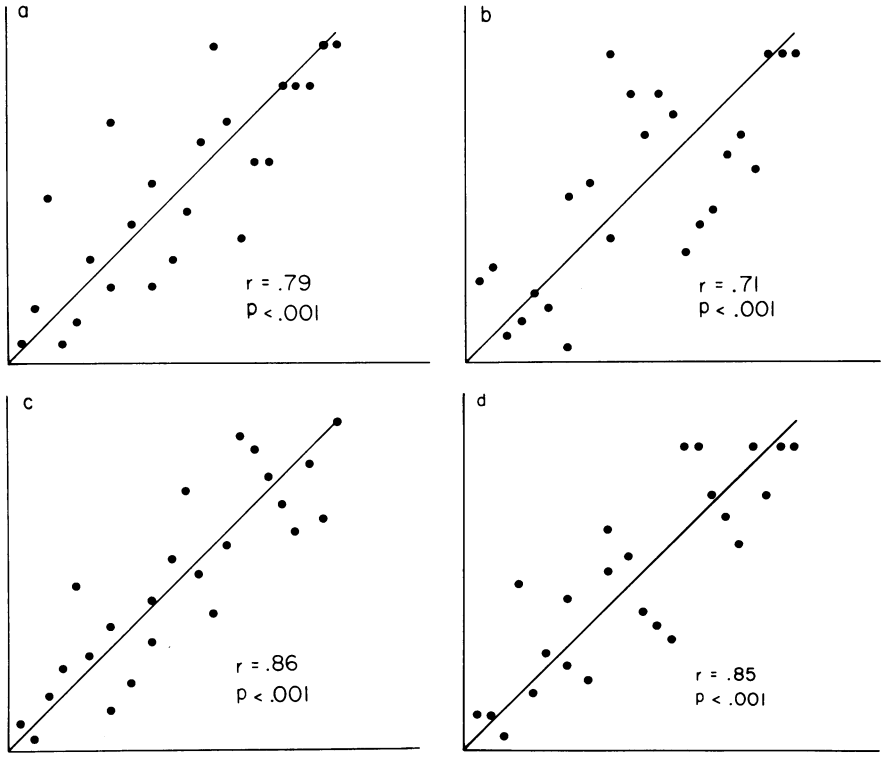

Figure 1. Correlation scattergrams between individual evaluators and the average subjective ranking: (a) Average vs JL. (b) Average vs EC. (c) Average vs AH. (d) Average vs BM. Straight line indicates perfect correlation (r = 1.00)

One might assume that patient age would be a primary determinant of perceived severity of disease, since older patients are more likely to have had multiple clinical manifestations of sickle cell disease. However, this is not the case. There is no correlation of patients ranked by subjective severity or quantitative indices and ranked by age ($P > .10$ by the Spearman rank correlation statistic).

In a preliminary report of the Index I objective classification,[8] the patients examined were graded as mild (0 to 4 points), moderate (4 to 8 points) or severe (over 8 points). On this basis, the mild:moderate:severe ratio among 71 patients was 45:30:25. Using the same definition, the mild:moderate:severe ratio in our sample was 15:15:70, clearly skewed to the severe side ($\chi^2 = 16$, $P < .005$). It did not seem likely that our random patient selection was biased toward those with severe disease. Therefore, this division of the study group into mild to severe classes was more closely examined.

Presently, in contrast to the earlier study, many of our patients are detected by newborn screening. Therefore, the age at diagnosis lacks any significance for clinical severity, since diagnosis is made at birth prior to any symptomatology. If the age factor is removed from the clinical classification criteria, the mild:moderate:severe ratio becomes 20:50:30. This ratio is not significantly different from that in the original report ($\chi^2 = 4.95$, $P > .05$).

It must be recognized that a ranking method such as discussed here cannot define severity for an individual patient. However, it is clear that, in principle, an index can be constructed for a group of patients to establish an order of disease severity acceptable to patient care providers. The objective classification indices given here satisfy this criterion. They could be an acceptable starting point for longitudinal patient evaluation, examination of effects of therapy, or correlation with laboratory or hematologic parameters so as to develop a bet-

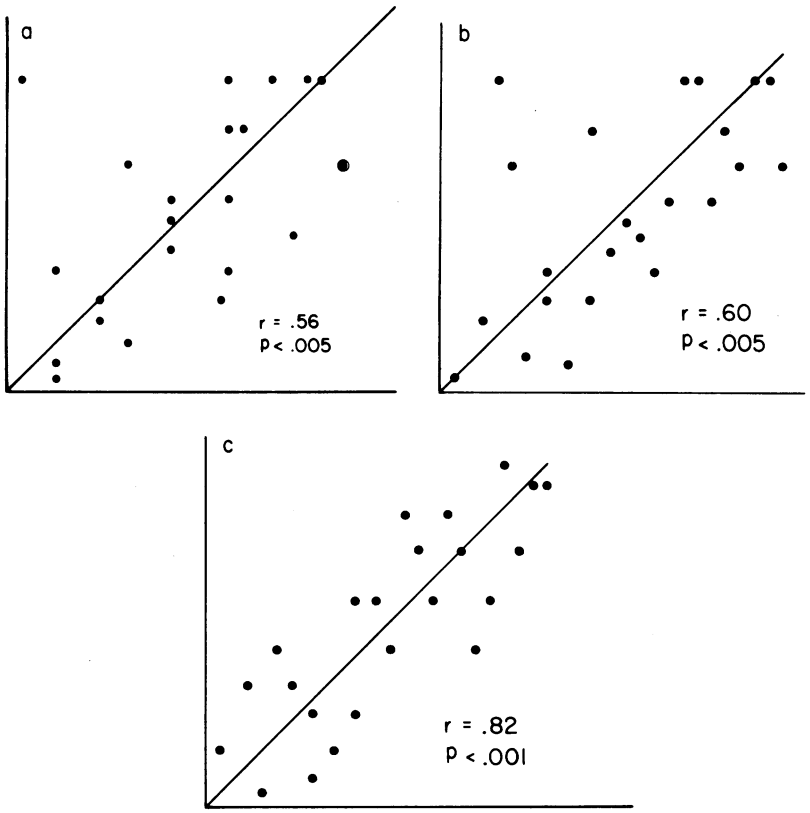

Figure 2. Correlation scattergrams between ranking by quantitative objective index and the average subjective ranking: (a) Index II vs Index I (⊙, 2 cases). (b) Index II vs average. (c) Index I vs average. Straight line indicates perfect correlation (r=1.00)

ter quantitative index. This process of using a rank correlation of evaluators to validate a quantitative (numerical) index or classification has been used in other clinical situations. It is similar to validation criteria for classification of malignancies for therapy or prognosis.[10]

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